Front-Line Trials and Current Landscape

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The Challenge of Treating Advanced/Recurrent Endometrial Cancer

• Despite frequent initial-or subsequent—treatment responses, prolonged remission or curative intent remain elusive for most patients with metastatic solid tumors

• Greatest contributor to cancer mortality: treatment-resistant, metastatic disease

• 5-year survival for patients with advanced/recurrent endometrial cancer disease 15-20%
  o Carboplatin/paclitaxel (C/P): standard of care
  o C/P alone in GOG/NRG Oncology trials: Median PFS rates of patients with biomarker unselected or mismatch repair proficient tumors ~8-13 months
  o High-grade or measurable disease, tumors with rare histologies, non-Hispanic Black women

• The reality: cytotoxic chemotherapy is only moderately effective in EC

• Tumoral molecular/mutational profile is key
New Developments in Endometrial Cancer

FDA Approvals for Endometrial Cancer

- Megestrol acetate (1955)
- Medroxyprogesterone Acetate (1975)
- Pembrolizumab (dMMR, tissue) (加速批准 2015)
- Lenvatinib + pembrolizumab (加速批准 2019)
- Dostarlimab (加速批准 2021)
- Dostarlimab + C/T (dMMR, 2/9/23)

Clinical Trials for Endometrial Cancer (Phase 2, Phase 3) by Start Date

- 2013: 5
- 2014: 9
- 2015: 11
- 2016: 13
- 2017: 21
- 2018: 23
- 2019: 19
- 2020: 22

Courtesy of Stephanie Gaillard, MD, PhD
A Decade of Practice-Changing Advancements in the Treatment of Advanced-Stage Endometrial Carcinoma

**Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial**

Davies MA, MD; Virginia Filice, PhD; Marcus E Powell, MD; David Mab, MD; Margaret M Steinhef, MD; Paul A Dijkstra, MD; Katherine M. Malley, M.D.; Yong M. Kim, MD; Ph.D.; Matthew A. Powell, M.D.; David N. O'Unity, M.D.; Niki M. Spiteri, M.D; William Small, Jr., M.D.; et al.

**Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosamide in Patients With Carcinoma of the Uterus or Ovary: An NRG Oncology Trial**

Matthew A. Powell, MD; Virginia L. Filice, PhD; Maret L. Hendry, MD; Helen G. Huang, MD; Katherine N. Moore, MD; Kristinenne M. Tran, MD; Larry J. Concannon, MD; Angelo A. Testore, MD; David E. Mullich, MO; Alexandre Font, MO; David P. Marshall, MD; Niki M. Spiteri, MD; Paul A. Dijkstra, MD; Olegs B. Ioffe, MD; MO and David S. Miller, MD.

**Carboplatin and Paclitaxel plus Avemal and compared with carboplatin and paclitaxel in advanced or recurrent endometrial cancer (MITO END-3): a multicentre, open-label, randomised, controlled, phase 2 trial**

Sandra Pignata, MD, PhD; Prof Giovanni Scambia, MO; Corrado Schettini, MO; Laura Annare, MS; Carmela Picano, MO; Davide Lombardi, MO; et al. Show all authors • Show notes

**Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer**

Ramesh N. Balander, MD; Michael W. Shi, PhD; Linda Belford, MD; Michael Goode, MD; Yarlla M. Hope, MD; Ferdinand B. Miras, MD; Robert M. Merlot, MD; Waik S. Shaha, MO; Catherine H. Cantu, MO; Eugena Girds, MO; Coni Michos, MO; John Kowalski, MO.

**Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase 3 DUO-E Trial**

Sharon K. Wedo, MD, MPH; Kathleen Moore, MD Hubeck; Cheng Lin, MD; Jessica Thorne Regis, MO; Michael Gandhorn, MO; Ayad Shou, MO, PhD. External content: doi:10.1002/ONCO.2020.03.003

**Randomized Phase II Trial of carboplatin-paclitaxel compared to carboplatin-paclitaxel-trastuzumab in advanced (stage III-IV) or recurrent uterine serous carcinomas that overexpress Her2/Neu (NCT01367002): updated overall survival analysis**

Amanda N. Fader, MD; Dana M. Roque, MD; Eric Siegel, MO; Natalia Buzaia, MD; Pei Hu, MD; Osama Abdelghany, MD; Setsuko Chambers, MD; Angela Aravena Secord, MO; Laura Havivlys, MO; David M. O'Malley, MO; Floor J. Bockers, MO; Nicole Navadzky, MO; Babak Eshaki, MO; Dirk Piekart, MD; David W. Loney, MO; Karin Ellahal, MO; Paul Celano, MO; Stefania Bellona, MO; Measad Aoun, MO; Babak Lihatko, MD; Elena Ratner, MD; Ananis Silvax, MO; Peter E. Schwartz, MO; Alessandro D Santino, MO.
Mutation Spectra Across Endometrial Carcinomas

- Mismatch repair proficient (pMMR) HER2 and/or p53 overexpressed/mutated tumors have the worst prognosis

- We must focus our efforts on drug development and novel synergistic combination strategies in this patient population

PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center)

- DNA MMR protein Immunohistochemistry
  - Expression lost
  - Expression retained
    - p53 immunohistochemistry
      - Normal/Wild-type pattern
      - Aberrant/Mutant pattern
        - MSI-H
        - Copy number-low
        - Copy number-high

- POLE sequencing
  - POLE hotspot mutation
  - No POLE hotspot mutation

- MMR IHC missing
  - MMR deficient
  - MMR intact

- NSMP/p53wt
- p53 IHC missing
- p53abn

Talk Objectives

- Appraise the current clinical trials landscape in the treatment of advanced endometrial carcinoma
- Review how novel treatment options targeting tumor-specific biomarkers have ushered in a new era of precision and personalized cancer therapeutics
- Discuss where we go from here in practice and trial design: can we clarify post-surgery or first-line recurrence treatment strategies for you?

- Choice Overload!
- The paradox of choice
PORTEC-3 Study Design

Key eligibility criteria:
- Newly diagnosed endometrial carcinoma s/p TAH/BSO +/- LND
- Stage I, endometrioid grade 3 with deep myometrial invasion or LVSI (or both)
- Endometrioid stage II or III
- Stage I-III with serous or clear cell histology (IA with +MI)
- No residual disease

De Boer et al, Lancet Oncol, 2019
PORTEC-3 Results

Overall survival and failure-free survival

Serous carcinoma (stage III)
- 5-year failure-free survival: 56.7% (chemoRT) vs 47.9% (RT)
  HR 0.42 (95% CI 0.22–0.80)
- 5-year overall survival: 71.4% (chemoRT) vs 52.8% (RT)
  HR 0.46 (95% CI 0.24–0.82)

GOG 258 Study Design

Key eligibility criteria:
- Newly diagnosed III/IV endometrial carcinoma or I/II serous/clear cell with cytology
- Curative intent TH/BSO +/- LN sampling/dissection
- <2 cm residual disease

- XRT 45Gy in 25 fx
- Cisplatin 50 mg/m2 D1 + 29 +/- Vaginal brachytherapy
- Carboplatin (AUC 6)
- Paclitaxel 175 mg/m² (Q3W, 6 cycles)
- Carboplatin AUC 5-6
- Paclitaxel 175mg/m2 q3 weeks X 4 cycles

Primary Endpoints:
- Relapse Free Survival (DFS) - Investigator

Secondary Endpoints:
- Overall survival
- Safety
- QoL

SGO 2023 Annual Meeting: Recurrence-free survival was not improved with the combination over chemotherapy alone. After a median follow-up of 112 months, the HR for overall survival with chemoradiotherapy (CRT) was 1.05. Local recurrences better with CRT, but increased distant recurrences.

PORTEC-3 and GOG 258 molecular analyses

<table>
<thead>
<tr>
<th>TCGA group</th>
<th>n</th>
<th>Treatment</th>
<th>5-yr RFS</th>
<th>HR (95% CI)</th>
<th>5-year OS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53abn</td>
<td>93</td>
<td>EBRT versus CisRT + chemo</td>
<td>36.2%</td>
<td>1 (0.52 0.30-0.91)</td>
<td>41.8%</td>
<td>1 (0.55 0.30 1.00))</td>
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<tr>
<td>POLEmut</td>
<td>51</td>
<td>EBRT versus CisRT + chemo</td>
<td>96.6%</td>
<td>1 (&lt;0.01 0.01-10^5)</td>
<td>96.6%</td>
<td>1 (&lt;0.02 0.01-10^3)</td>
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<tr>
<td>MMRd</td>
<td>137</td>
<td>EBRT versus CisRT + chemo</td>
<td>75.5%</td>
<td>1 (1.29 0.68-2.45)</td>
<td>84%</td>
<td>1 (1.33 0.64-2.75)</td>
</tr>
<tr>
<td>NSMP</td>
<td>129</td>
<td>EBRT versus CisRT + chemo</td>
<td>67.7%</td>
<td>1 (0.68 0.36-1.3)</td>
<td>87.6%</td>
<td>1 (0.68 0.26-1.77)</td>
</tr>
</tbody>
</table>


Relapse-Free Survival based on modified ProMiSe Algorithm

Molecular Status

Clements et al, IGCS 2023
Phase II Randomized
1° End-Point: PFS
N= 349

Eligibility:
- Stage III or IVA EC measurable disease
- Stage IVB or Recurrent EC (whether there is measurable disease or not)
- No prior Chemotherapy

Arm 1:
- Paclitaxel 175 mg/m2 IV over 3 hours day 1
- Carboplatin AUC = 6 IV day 1
- **Bevacizumab 15mg/kg IV day 1**
- Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or prohibition of further therapy.

Arm 2:
- Paclitaxel 175 mg/m2 IV over 3 hours day 1
- Carboplatin AUC = 5 IV day 1
- **Temsirolimus 25 mg IV days 1 and 8**
- Maintenance regimen – Temsirolimus 25 mg IV weekly. Days 1, 8 and 15 until disease progression or prohibition of further therapy.

Arm 3:
- **Ixabepilone 30 mg/m2 IV over 1 hour day 1**
- Carboplatin AUC = 6 IV day 1
- **Bevacizumab 15mg/kg IV day**
- Maintenance regimen - Bevacizumab 15mg/kg IV every 21 days until disease progression or prohibition of further therapy.

PI: Carol Aghajanian, M.D.
From: 9/14/2009 to 9/9/2014
ClinicalTrials.gov Identifier:NCT00977574
From GOG Study 86P Survival by Treatment Group Integrated for Missense TP53 and IHC p53 Over-Expressed (IHC for p53 may serve as a predictive biomarker for bevacizumab upfront + chemotherapy, Thiel...Leslie, JCO, 2022).

55 of 213 (26%) of the patients on GOG 86P met the criteria to be classified within this group.

p53 Over-Expressed (OE) staining by IHC

Median Overall Survival 30.0 months on bevacizumab + chemo versus 14.4 months for temsirolimus + chemo, a significant improvement in outcomes for a high risk patient group with generally poor OS with standard therapy.

OS Hazard Ratio 0.28 [0.14-0.59] when bevacizumab is given upfront with chemotherapy.
Why are mutations in p53 potentially relevant to bevacizumab + chemotherapy sensitivity?

- **Cell cycle checkpoint abrogation**: Cells with mutated p53 lack the normal cell cycle checkpoints, preventing DNA repair. This makes cancer cells **more vulnerable to chemotherapy**.

- **Angiogenesis**: Mutated p53 enhances VEGF expression and tumor angiogenesis, making cells **more vulnerable to antiangiogenics**.

Courtesy of Dr. Kim Leslie
From The Medical Biochemistry Page
**P53 wild type maintenance therapy**

**GOG-3055/ENGOT-EN5/SIENDO (NCT03555422)**

- Selinexor, a first-in-class oral selective inhibitor of the nuclear export compound that selectively binds to nuclear protein exportin 1 and inhibits its export, and blocks the nuclear export of tumor suppressor, growth regulatory, and anti-inflammatory proteins
- Phase 3, multicenter, double-blind, placebo-controlled, randomized study; **maintenance after chemotherapy** (stage IV or recurrent endometrial cancer); N=263
- Selinexor 80 or 60 mg on days 1, 8, 15, and 22 of each 28-day cycle
- Primary endpoint: median PFS 5.7 vs 3.8 months; HR 0.70 (p=0.0486)
- In pre-specified subgroup of p53wt: median PFS 13.7 vs 3.7 months; HR 0.38 (p=0.0006)

Vergote, JCO 2023

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**ENGOT-EN5/GOG-3055/SIENDO**

- XPO1 exports the major tumor suppressor proteins away from the nucleus
- Cancer cells
  - Overexpress XPO1
  - Inactivate cytoplasmic p53 through protein degradation
- Selinexor inhibits XPO1 nuclear export
  - Leads to retention and reactivation of TSPs in the nucleus and stabilization of p53
  - Results in selective killing of cancer cells

Makker et al, JCO, 2022
P53 restoration of p53 mediated apoptosis

KRT-232-11: Navtemadlin
Phase 2/3 Study of Navtemadlin as Maintenance Therapy in Subjects with TP53WT Advanced or Recurrent Endometrial Cancer Who Responded to Chemotherapy 8/GOG-3089

- Oral MDM2 inhibitor
- Restores p53 activity to drive apoptosis of wild type TP53 cells
- Expression of pro-apoptotic Bcl-2 family proteins
Treatment Based Upon Molecular Make Up: HER2

- *Her2/neu* overexpression by IHC demonstrated in 14-60% of USC. Estimates vary widely due to lack of standardized algorithms for interpretation and scoring of *Her2* immunostains in endometrial cancer.

- Dysregulation of *Her2/neu oncogene* reported in 27% of USC in Whole Exome Sequencing (WES) studies performed by TCGA network (Levine DA, Nature 2013).

- HER2/neu functions as preferred partner for heterodimerisation with any of the other members of the EGF receptor family (HER1, HER3 and HER4) and responsible for regulating cell growth and differentiation.
Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu


Study Design

- 61 patients with advanced stage/recurrent HER2+ USC
- 3+ IHC, or 2+ with FISH + (modified 2007 ASCO/CAP)
- Measurable/non-measurable disease
Improvement in PFS and OS for Advanced-Stage Disease with Addition of Trastuzumab

Fader AN, JCO, 2018

Fader AN, Clin Cancer Res, 2020
NRG GY-026

Newly Diagnosed, Stage I-IVB, HER2 positive uterine serous or carcinosarcoma

Randomize 1:1:1

Arm 1:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles (may continue to 10 cycles if measurable disease and SD or PR)

Arm 2:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + trastuzumab 8 mg/kg IV loading dose f/b 6 mg/kg IV q 21 days

Arm 3:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ (with initial 1200 mg SQ pertuzumab loading dose w 1st cycle)

Maintenance trastuzumab 6mg/kg IV every 21 days x 1 year (or progression/prohibitive toxicity)

Maintenance fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ q 21 days for 1 year (or until disease progression or prohibitive toxicity)

PI: Britt Erickson
Co-PI: Amanda Fader
Intl Co-PI: Clare Scott
Transl PI: Alessandro Santin

Strata:
- Stage (I-II vs III-IV)
- Measurable vs. non-measurable dz
- Histology (serous vs carcinosarcoma)
Immune Checkpoint Inhibitor Therapy in Endometrial Cancer

Pembrolizumab (KN-158): Robust Antitumor Activity in Patients With MSI-H Advanced EC

<table>
<thead>
<tr>
<th>Variable</th>
<th>MSI-H EC n = 79</th>
<th>EC (biomarker unselected) n = 107</th>
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<tbody>
<tr>
<td>ORR % (95% CI)</td>
<td>48 (37-60)</td>
<td>11.2 (5.9-18.8)</td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>27 (34)</td>
<td>12 (11.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>14 (18)</td>
<td>26 (24.3)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23 (29)</td>
<td>56 (52.3)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>1 (1)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td>Not assessed</td>
<td>3 (4)</td>
<td>11 (10.3)</td>
</tr>
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</table>

Dostarlimab (GARNET Cohorts A1 & A2): Clinical Benefit in dMMR and MMRp EC Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>dMMR EC n = 103</th>
<th>MMRp EC n = 142</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR % (95% CI)</td>
<td>46 (34.9-54.8)</td>
<td>19 (8.3-20.1)</td>
</tr>
<tr>
<td>Complete response</td>
<td>11 (10.7)</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Partial response</td>
<td>35 (34.0)</td>
<td>16 (11.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>13 (12.6)</td>
<td>31 (21.8)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>39 (37.9)</td>
<td>77 (54.2)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Not done</td>
<td>2 (1.9)</td>
<td>15 (10.6)</td>
</tr>
</tbody>
</table>

*Marabelle, J Clin Oncol 2020*
In the era of targeted and immunotherapies, how can we improve response to both cytotoxic chemotherapy and immunotherapies?

How can we improve response to checkpoint inhibitors?

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Chemotherapy has been shown to:

- Enhance antigen presentation
- Enhance immunogenicity (release of adjuvants by cells)
- Increase susceptibility to immune attack

Because of high recurrence rates, a variety of maintenance/consolidation strategies following completion of first-line chemotherapy have been tested.

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Courtesy of Dr. Rebecca Arend
NRG-GY018

Study Design

Key Eligibility Criteria
- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent endometrial cancer
- Pathology report showing results of institutional MMR IHC testing
- ECOG PS 0, 1, or 2
- No prior chemo except prior adjuvant chemo if completed ≥12 mo before study

Stratification Factors
- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

Endpoints
- Primary: PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- Secondary: Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of MMR IHC testing at institution vs centralized

Median follow-up:
- IA1 data cutoff date of December 16, 2022: dMMR cohort, 12 months; pMMR cohort, 7.9 months
- Current analysis data cutoff date of August 18, 2023: dMMR cohort, 20.6 months; pMMR cohort, 15.8 months
ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)
Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients
- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification
- MMR/MSI status
- Prior external pelvic radiotherapy
- Disease status

Dostarlimab IV 500 mg
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m² Q3W for 6 cycles

Dostarlimab IV 1000 mg
Q6W up to 3 years

Placebo IV
Carboplatin AUC 5 mg/mL/min
Paclitaxel 175 mg/m² Q3W for 6 cycles

Placebo IV
Q6W up to 3 years

Primary endpoints
- PFS by INV per RECIST v1.1
- OS

Secondary endpoints
- PFS by BICR per RECIST v1.1
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

Follow-up


Treatment ends after 3 years; PD, toxicity, withdrawal of consent, investigator’s decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; E5, endometrial cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HRQOL, health-related quality of life; HIC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
AtTEnd Study Design

- Endometrial carcinoma or carcinosarcoma
- Patients with advanced (stage III-IV) newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence.
- In recurrent patients, one prior line of systemic platinum-based regimen is permitted with a platinum-free interval ≥ 6 months.
- ECOG 0-2
- Normal organ and bone marrow function

Endpoints

- Stratified by:
  - Country
  - Endometrioid vs. other histotypes
  - Recurrent disease vs newly diagnosed
  - dMMR vs dMMR vs non evaluable (centrally evaluated)

HR: 0.5
PFS
dMMR
α (two-sided) 4%

HR: 0.7
PFS
All comers
α (two-sided) 4%

OS*
All comers
α (two-sided) 5%


*OS interim analysis planned with a 63% power

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DUO-E study design

Patients
- Newly diagnosed FIGO 2009 Stage II/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas

Endpoints

Primary
- PFS (RECIST per investigator) in:
  - Durva vs Control
  - Durva+Ola vs Control

Key secondary
- OS (analytical)
- Safety

Exploratory
- PFS in Durva+Ola vs Durva
- Subgroup analyses of PFS
  - Including MMR, PD-L1, and HRRm

Stratified by:
- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs non-Asia)

Treatment until disease progression, unacceptable toxicity or other discontinuation criteria were met

Control
- N=718
- R 1:1:1
- CP* (q3w) + Durvalumab pbo (IV q3w)

Durva
- CP* (q3w) + Durvalumab (1120 mg IV q3w)

Durva+Ola
- CP* (q3w) + Durvalumab (1120 mg IV q3w)

Maintenance phase
- Durvalumab pbo (IV q4w) + Olaparib pbo (tablets bid)

Durvalumab pbo (IV q4w) + Olaparib pbo (tablets bid)

Cytotoxic drugs used:
- Carboplatin
- Paclitaxel

*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m².
- bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation;
- IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

Shannon N. Westin

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<table>
<thead>
<tr>
<th>GY018 (816 pts)</th>
<th>RUBY (494 pts)</th>
<th>AtTEnd (550 pts)</th>
<th>Mito End-3 (125 pts)</th>
<th>Duo-E (718 pts)</th>
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<tbody>
<tr>
<td><strong>Experimental Arm(s)</strong></td>
<td>Pembrolizumab (PD-1)</td>
<td>Dostarlimab (PD-1)</td>
<td>Atezolizumab (PDL1)</td>
<td>Avelumab (PDL1)</td>
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<tr>
<td><strong>Study design; primary endpoint</strong></td>
<td>RP3; PFS in parallel dMMR &amp; pMMR cohorts</td>
<td>RP3; PFS and OS</td>
<td>RP3; PFS and OS</td>
<td>RP2; PFS</td>
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<td><strong>Measurable or evaluable Stage III/IV</strong></td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td><strong>Non-measurable Stage IVB</strong></td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
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<tr>
<td><strong>Serous, Clear-Cell, Mixed Histologies</strong></td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<td><strong>Carcinosarcoma</strong></td>
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<td>NO</td>
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<td><strong>Recurrent Disease (%)</strong></td>
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<td><strong>Prior Radiation</strong></td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td><strong>Prior Chemotherapy</strong></td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
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<tr>
<td><strong>Time Since Adjuvant Chemo</strong></td>
<td>≥12 months</td>
<td>≥6 months</td>
<td>≥6 months</td>
<td>≥6 months</td>
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<tr>
<td><strong>Duration of maintenance therapy</strong></td>
<td>14 cycles (~2 years)</td>
<td>3 years</td>
<td>Disease progression, toxicity, or other indication</td>
<td>Disease progression, toxicity, or other indication</td>
</tr>
</tbody>
</table>

Modified from Drs Arend and Backes
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in dMMR Tumors

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Sandro Pignata et al. The Lancet Oncology 2023, Nicoletta Colombo et al. ESMO 2023

Courtesy of Christian Marth, MD
Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in pMMR Tumors

Courtesy of Christian Marth, MD

NRG-GY018
HR 0.54
P<0.0001

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Sandro Pignata et al. The Lancet Oncology 2023, Nicoletta Colombo et al., ESMO 2023
OS Data: No benefit in All Comers-Ruby, AtTEnd, Mito End-3
RUBY Molecular Classification Algorithm

- In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients.

EC
(histological subtype independent)

POLE status
- POLE pathogenic
- POLE non-pathogenic

MMR status
- dMMR
- MMRp

p53 status
- P53-mut
- P53 WT

Integrated diagnosis
- POLε mut (EDM)
- dMMR (or MSI-H)
- TP53 aberrant
- NSMP

Prevalence in RUBY (nN)
1.25% (5/400)
22.75% (91/400)
22% (88/400)
54% (216/400)

Diagnostic test
- WES
- Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization

PFS According to Molecular Subgroup

HR, 0.31
(95% CI, 0.17–0.56)

HR, NA
(95% CI, NA–NA)

HR, 0.55
(95% CI, 0.3–0.96)

HR, 0.77
(95% CI, 0.55–1.07)

Data based on exploratory analysis based on 400 patients from the RUBY trial with known molecular classification with whole exome sequencing.

POLε, mismatch repair deficient; IHC, Immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; mut, mutated; NGS, next generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε, polymerase epsilon; SCNA, somatic copy number alterations; TIL, tumor infiltrating lymphocytes; TLS, tertiary lymphoid structures; TP53, tumor protein 53; WES, whole exome sequencing; WT, wild type.
## Consistent PFS Benefit in Histological Subgroups

<table>
<thead>
<tr>
<th>Histology</th>
<th>Dostarlimab + carboplatin-paclitaxel (no. of events/no. of patients)</th>
<th>Placebo + carboplatin-paclitaxel (no. of events/no. of patients)</th>
<th>Hazard ratio (95% CI)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid carcinoma</td>
<td>64/130</td>
<td>89/136</td>
<td>0.65 (0.473–0.902)</td>
<td></td>
</tr>
<tr>
<td>Carcinosarcoma</td>
<td>14/24</td>
<td>18/22</td>
<td>0.56 (0.278–1.138)</td>
<td></td>
</tr>
<tr>
<td>Serous adenocarcinoma</td>
<td>36/55</td>
<td>35/48</td>
<td>0.65 (0.403–1.035)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>21/36</td>
<td>35/43</td>
<td>0.58 (0.335–0.997)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratios are based on unstratified Cox regression model. 
CP, carboplatin-paclitaxel; HR, hazard ratio; PFS, progression-free survival.

Dr Mansoor Raza Mirza

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NRG GY018: Phase 3 Trial of Pembrolizumab + Chemo for Measurable Stage 3 or 4a, Stage 4b, or Recurrent EC – Subgroup Analyses of PFS

PFS per RECIST v1.1 in pMMR Population

PFS by Histology in pMMR Population

<table>
<thead>
<tr>
<th>Histology</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid, G1 or G2</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>Endometrioid, G3</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Other Types</td>
<td>128</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>586</td>
<td></td>
</tr>
</tbody>
</table>

Efficacy curves in the two MMR cohorts separated early in treatment, with a preserved separation throughout the evaluation period. Benefit was observed in most subgroups, including among patients who had received previous adjuvant chemotherapy or radiation, among those with less common histologic subtypes and in patients who identify as Black or White.

Data cutoff: December 16, 2022.
Durability of Response in Patients on GY018-Placebo

Central dMMR Waterfall Plot

Central pMMR Waterfall Plot
Durability of Response in Patients on GY018-Pembrolizumab
NRG-GY018 Ad hoc Analyses

PFS by Methylation Status in dMMR Population

**Methylation**

**Pembro + CP vs Placebo + CP**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + CP</td>
<td>51/77</td>
<td>7.5 (6.4-11.3)</td>
<td>0.307 (0.19-0.49)</td>
</tr>
<tr>
<td>Pembro + CP</td>
<td>28/83</td>
<td>NR (22.3-NR)</td>
<td></td>
</tr>
</tbody>
</table>

**No Methylation**

**Pembro + CP vs Placebo + CP**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (95% CI), mo</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + CP</td>
<td>11/17</td>
<td>8.3 (4.4-NR)</td>
<td>0.263 (0.07-0.99)</td>
</tr>
<tr>
<td>Pembro + CP</td>
<td>3/13</td>
<td>NR (14.2-NR)</td>
<td></td>
</tr>
</tbody>
</table>

**Methylation Status**

**Pembro + CP Arm**

<table>
<thead>
<tr>
<th>Events</th>
<th>Median (95% CI), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + CP</td>
<td>NR (14.2-NR)</td>
</tr>
<tr>
<td>Pembro + CP</td>
<td>NR (22.3-NR)</td>
</tr>
</tbody>
</table>

---

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## Subgroup analysis of PFS: Durva+Ola vs Control

By stratification factors and biomarker status

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Durva+Ola n/N (%)</th>
<th>Control n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>0.53 (0.42–0.67)</td>
<td>126/239 (52.7)</td>
<td>173/241 (71.8)</td>
</tr>
<tr>
<td><strong>Disease status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>0.47 (0.33–0.66)</td>
<td>58/114 (50.9)</td>
<td>81/115 (70.4)</td>
</tr>
<tr>
<td>Recurrent disease</td>
<td>0.59 (0.43–0.81)</td>
<td>68/125 (54.4)</td>
<td>92/126 (73.0)</td>
</tr>
<tr>
<td><strong>MMR status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proficient tumours</td>
<td>0.57 (0.44–0.73)</td>
<td>108/191 (56.5)</td>
<td>148/192 (77.1)</td>
</tr>
<tr>
<td>Deficient tumours</td>
<td>0.41 (0.21–0.75)</td>
<td>18/48 (37.5)</td>
<td>25/49 (51.0)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>0.68 (0.44–1.06)</td>
<td>37/67 (55.2)</td>
<td>45/68 (66.2)</td>
</tr>
<tr>
<td>Non-Asia</td>
<td>0.48 (0.36–0.63)</td>
<td>89/172 (51.7)</td>
<td>128/173 (74.0)</td>
</tr>
<tr>
<td><strong>HRRm status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRRm</td>
<td>0.30 (0.15–0.58)</td>
<td>16/39 (41.0)</td>
<td>23/32 (71.9)</td>
</tr>
<tr>
<td>Non-HRRm</td>
<td>0.59 (0.44–0.80)</td>
<td>81/141 (57.4)</td>
<td>96/132 (72.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.57 (0.36–0.89)</td>
<td>29/59 (49.2)</td>
<td>54/77 (70.1)</td>
</tr>
<tr>
<td><strong>PD-L1 expression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (TAP score ≥1%)</td>
<td>0.42 (0.31–0.57)</td>
<td>68/150 (45.3)</td>
<td>114/163 (69.9)</td>
</tr>
<tr>
<td>Negative (TAP score &lt;1%)</td>
<td>0.80 (0.55–1.16)</td>
<td>55/82 (67.1)</td>
<td>57/75 (76.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>NC (NC–NC)</td>
<td>3/7 (42.9)</td>
<td>2/3 (66.7)</td>
</tr>
</tbody>
</table>

Stratification factors (disease status, MMR status, and geographic region) are per the randomisation code. PD-L1 status in baseline tumour tissue was determined centrally using Ventana PD-L1 SP263 immunohistochemistry assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumour area populated by tumour cells or immune cells with membranous PD-L1 staining. HRRm status was assessed in baseline tumour tissue using the Foundation One CDx NGS assay and includes a mutation in any of these genes: ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing.

Shannon N. Westin

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**Background – Rational**

- Advanced and metastatic (M+) EC is an heterogeneous tumor.
- Many of advanced EC tumors have significant deficiencies in DNA repair pathways.
- P53 mutations are associated with high Copy Number Alterations (CNA).
- Homologous replication deficiency (HRD) is significantly associated with P53 mutated EC.

→ Frequent high DNA damage suggests the possibility to use PARP inhibitors as maintenance after chemotherapy.

**UTOLA study design**

**Randomized phase II trial**

**INDICATION OF CHEMOTHERAPY**

- Advanced or Metastatic Endometrial Cancer
- Endometrioid, clear cells, serous and mixed histologies
- Adjuvant CT allowed (f > 1 yr)

**Platinum based CT**

- 6 cycles

**NED CR PR SD**

- **Advanced or Metastatic Endometrial Cancer**

**Inclusion = 2 years**

- **Olaparib maintenance n=98**
- **Placebo maintenance n=49**

**Untill PD**

**2:1**

**Stratification factors**

- PS3 and MMR status
- Response to previous CT

**Primary endpoint : PFS in the ITT Population**

- Endpoint: Improvement of median PFS from 4.5 months to 7.5 months (from randomization)

**Main secondary endpoints**

- PFS according to P33 status
- PFS according to response rate
- OS in ITT and according to P53 status
- Safety
- (QoL)

**Pre-specified other secondary endpoint**

- PFS according to HRD status

**UTOLA objectives**

- **Objectives**
- **Endpoints**

---

**Joly-Lobbdez ESMO 2023**

**GINECO**

**GOG FOUNDATION**

**ESMO**

**ESMO congress**

**RESIST 1:1**

**RESIST 2:1**
Utola PFS: ITT

PFS* by investigator assessment: ITT

N=147

median follow-up = 31 mo

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n=98)</th>
<th>Placebo (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (months) [95% C.I.]</td>
<td>5.62 [3.71; 8.84]</td>
<td>3.98 [3.48; 7.66]</td>
</tr>
<tr>
<td>HR</td>
<td>0.94 [0.65 - 1.35]</td>
<td>p=0.360</td>
</tr>
</tbody>
</table>

PFS calculated from randomization (end of CT)

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>0</td>
<td>98</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>9</td>
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<td>24</td>
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<td>27</td>
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<td>4</td>
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<td>4</td>
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<td>33</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

[Graph showing Kaplan-Meier curves for PFS by treatment group, with key statistics and event probabilities listed below the graph.]
Utola PFS by p53, HRD, or Both

PFS by investigator assessment: P53 status

PS3 mut – n= 78
PS3 WT – n= 68

PFS: HRD (LGE ≥6) and P53mut (exploratory analysis)
LGE ≥6, pMMR, P53 mut n=56

PFS: According to HRD status

HRD (LGE ≥8) n = 73
HRp (LGE <8) n = 67
**ENGOT-en9/A-AGO:** A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) Versus Chemotherapy for First-line Treatment of Persistent, Recurrent, or Metastatic Endometrial Carcinoma (LEAP-001)

- Stage III, IV or recurrent endometrial carcinoma
- No prior chemotherapy (except chemoradiation)
- ECOG 0 or 1
- 888 randomized patients

**Stratify:**
- MMR status (pMMR vs. dMMR)
  - If pMMR,
    - ECOG (0 versus 1)
    - Measurable disease (yes vs. no)
    - prior chemoradiation (yes vs. no)

**Treatment arms:**
- Pembrolizumab 200 mg IV infusion Q3W15 mg/kg q3w
  - Up to 35 infusions
- Lenvatinib 20mg orally QD
- Carboplatin AUC 6 (-5) IV infusion Q3W
  - Up to 7 cycles
- Paclitaxel 175 mg/m² IV infusion Q3W
  - Up to 7 cycles

Christian Marth et al. Int J Gynecol Cancer 2021
001 Trial Evaluating KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) as First-Line Treatment for Patients with Advanced or Recurrent Endometrial Carcinoma

RAHWAY, N.J., & NUTLEY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, and Eisai today announced that the Phase 3 LEAP-001 trial evaluating KEYTRUDA, Merck’s anti-PD-1 therapy, plus LENVIMA, the orally available multiple receptor tyrosine kinase inhibitor discovered by Eisai, did not meet its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) for the first-line treatment of patients with advanced or recurrent endometrial carcinoma whose disease is mismatch repair proficient (pMMR)/not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)/MSI-H.

At the final analysis, KEYTRUDA plus LENVIMA did not improve OS or PFS sufficiently to meet the study’s prespecified statistical criteria in the first-line treatment of certain patients with advanced or recurrent endometrial carcinoma versus a standard of care, platinum-based chemotherapy doublet (carboplatin plus paclitaxel). The safety profile of KEYTRUDA plus LENVIMA was consistent with that observed in previously reported studies evaluating the combination. A full evaluation of the data from this study is ongoing. The companies will work with investigators to share the results with the scientific community.
KEYNOTE-C93/GOG-3064/ENGOT-en15: A phase 3, randomized, open-label study of first-line pembrolizumab versus platinum-doublet chemotherapy in mismatch repair deficient advanced or recurrent endometrial carcinoma.

Phase 3 KEYNOTE C93:
First-Line Pembrolizumab vs Chemotherapy in dMMR

- Histologically confirmed stage III/IV recurrent EC including carcinosarcoma
- ECOG PS 0/1
- No prior systemic therapy
- dMMR

Stratification
- Disease status: newly diagnosed advanced EC vs recurrent EC
- Histology: endometrioid vs nonendometrioid

Pembrolizumab 400 mg IV Q6W

Paclitaxel 175 mg/m² IV Q3W + Carboplatin AUC 6 IV Q3W

- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DCR, DOR

N = 350

Courtesy of Shannon Westin, MD
Summary

• Remarkable progress in treatment of upfront advanced/first-line recurrent endometrial cancer (EC) based on advancements in molecular understanding and development of novel drugs that target specific tumoral mutations/aberrations and protein expression levels.

• Carboplatin/paclitaxel remains an important backbone of treatment for advanced/recurrent disease.
  - Only moderate and limited effectiveness, associated with relatively short PFS and high, unsalvagable recurrence rates.
  - Escalation/add-on trial strategies appropriate in this setting, especially when treating patients with pMMR, HER2 expressed/amplified, or p53 aberrant disease.

• Endometrial cancer has great genomic heterogeneity.

• Molecular profiling of EC tumors allows GYN and medical oncologists to realize the promise of precision-based medicine—several molecular biomarkers are prognostic and predictive.
  - Test all patients and test early!
  - Targeted therapy options based upon mismatch repair status and HER2.
  - Emerging therapeutic options for p53 aberrant v wildtype tumors and HRD positive EC.
  - Will molecular testing also allow for smarter radiation therapy strategies?

• Ongoing and future trials will help clarify optimal treatment.
Thank you

• GOG-F, Dr. Tom Herzog, Ms. Jenna Cummins, Ms. Cori Niskala, Ms. Lindsey Moeller

• Dr. Angeles Alvarez Secord

• Our patients

• All trial investigators, local trial PIs, colleagues enrolling